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THE CHEMICAL FACTOR IN DISEASE.

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With the Complements of Dr. Stamilton.

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## THE CHEMICAL FACTOR IN DISEASE.

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There are some factors in pathology evidently due to chemistry. Through improved methods of research the isolation and synthesis of putrescent alkaloids are rendered feasible, urinology simplified, and the detection and elaboration of animal approximates made possible.

The therapeutical effects of these bases point to them as sources of auto-infection and of the dissemination of disease.

Theories for the genesis of malady have been an alluring subject to physicians, and the disposition to fit cases to them is more frequently the error of the followers than of the originators of the postulates.

The eagerness with which the art of medicine grasps at the principles in science, to solve her problems, is shown by a glance at the natural development of her literature, until today the test-tube, balance, combustion furnace, and philosophical chemistry insist upon recognition.

The masters in physic from mere observation evolved a humoral pathology satisfactorily explaining to them the cause, cure of disease, and resulting death of the body.\* Upon the improvement in instruments of precision, clinical examinations were made with accuracy, and, when compared, gave rise to the experimental method in medical science; creating the cellular doctrine, whose optical responses to many processes of disease are esteemed conclusive. Subsequent investigation nurtured by chemico-optical tests led to the promulgation of the bacillar pathology.

Further scrutiny by crucial analytical researches determined that chemical approximates were capable of producing recog nized symptoms of disease, and readily demonstrated them as a cause of death.§ From this brief review we may expect soon

† Virchow's epoch.

§Selmi, Gautier, Brieger, and others.

<sup>\*</sup>Authors prior to Haller.

Pasteur, Koch, and others.

to find newly-hatched hypotheses, but the circle which they suggest demonstrates, conclusively, that the progress of medicine is ceaseless.

The urine, from its quantity, odor, appearance and sediments, has been an object of earnest study, and the interest is only more excited as delicate means of inquiry are known. The *inspection* of the urine is usually made to deceive the ignorant, the *analysis never*. The importance of urinology to semeiology is patent: by it we judge of general physiological processes, by it we detect the abundance or entire absence of eliminated approximate principles and also fix the dosage of drugs.

Simple volumetric schemes allow one to make rapidly an examination of the physical qualities, inorganic and organic, extractives, etc., of the urine. The sediments belong to uroscopy.

The following quick and sufficiently accurate method has in my hands been useful. Observe carefully the physical qualities of the urine with the daily (twenty-four hours) amount. Note the specific gravity; multiply its last three figures by 0.0233,\* which will give the percentage of solids.

Estimate the chlorides volumetrically (1 cubic centimetre) with nitrate of silver (4.788 grammes of pure nitrate of silver to 1000 cc. or grammes of pure water); 1 cc. equals 0.001 gramme of chlorine, or 0.00165 gramme of sodium chloride. The number of cc. used, therefore, multiplied by 0.165 will give the percentage of chlorides found.

For the phosphates, a volumetric solution of 34 grammes of acetate sesquioxide of uranium in 1000 cc. of water; 1 cc. of this solution is equal to 0.005 gramme of phosphoric acid, or 0.1 gramme of phosphates, so that if the number of cc. (say 50 of urine used) be multiplied by 0.2, the cc. of uranium solution used, the percentage of phosphates will be discovered.

The sulphates may be taken as about one-half the phosphates.

The urea may be easily determined by Ivon's method, § modified by Dr. Squibb. The principle is the changing of a solu-

<sup>\*</sup>Neubauer and Vogel, Anal. of Urine, p. 347.

<sup>†</sup> Parke's Hygeine (Wood & Co., N. Y.), vol. II, p. 380.

<sup>‡</sup> Neubauer and Vogel, p. 250.

<sup>§</sup> Neubauer and Vogel, p. 242 et seq.

tion of bromide into a bromite of potassa, and the decomposition of urea into carbonic acid, water and nitrogen by the addition of Labarraque's solution (of chlorinated soda); 1 gramme of urea yields 370 cc. of nitrogen, so that if 1 cc. of urine is used the calculation is easily made.\* A quantitative estimation of urea may be made in ten minutes.

For grape-sugar the use of Parke, Davis & Co.'s globules of Fehling's solution is most satisfactory; I have tested them repeatedly, and found them correct.

All these estimates may be made in half an hour; with ordinary care the reagents will keep unaltered a long time.

For each per cent. of an element in solution added to pure water the specific gravity is correspondingly increased.† For the constituents of the urine found, namely, the chlorides raise the specific gravity 8 degrees; the phosphates, 4 degrees; the sulphates, 5 degrees; the urea, 3 degrees; the glucose, 3 degrees. The difference between this result and the total solids mentioned before shows the other unknown extractives which vary with health. These extractives usually amount to about 7 or 8 per cent., and go to make up about 3 degrees of specific gravity. By applying this process the vital value of the extractives may be fixed. The results may be stated. For example, 1500 cc. in twenty-four hours, specific gravity 1023.23, multiplied by 0.0231, gives 5.313 as the per cent. of total solids to be found.

<sup>\*</sup>Messrs. Queen & Co., of Philadelphia, and Parke, Davis & Co., of Detroit, Mich., have apparatus for a dollar or so, with directions.

<sup>†1</sup> gramme of salt added to 1000 cc. of pure water will increase its specific gravity about 8°, and so for any other constituent of the urine accordingly. The application of this method is from a scheme used at the medical school of Netley, England, by Professor de Chaumont (recently deceased).

TABLE I.

ELEMENTS.	Per cent.	Specific gravity raised per ele- ment.	Total amount degrees sp. gr. per element in solution.	Am't in grammes in 1500 cc. per 24 hours.
Chlorides,	0.891	80	7.130	16.48
Phosphates,	0.320	4	1.28	5.92
Sulphates,	0.169	5	0.80	2.96
Urea,	2.000	3	6.00	37.00
Glucose,	1.190	3	4.76	22.01
Extractives (diff.),	0.758	4	3.03	14.02
	5.319		23.00	98.39

In 1842 Liebig wrote that physiologists were careless in their methods of research, and recommended the systematic plans of chemistry. He says:

"Detached observations are points scattered over a plain; for centuries chemistry could only present these points, showing no decided path."

To-day we have these points connected with arches of solid truth, which, in the smart progress of the age, classifies chemistry into those having a certain chemical composition, and those, again, having a chemical constitution.\*

All persons instinctively shrink from decaying carcasses, yet investigations into their disintegrations are demanded by science and the ends of justice. That spoiled meats are unwholesome is well known (botulism). The sad experience of medical students is that there are cadaveric poisons. The septic influence of wounds and the peculiar fevers of the lying in period have drawn attention to blood-poisoning.

In 1820 some bases of a very virulent type were extracted from corpses.† To isolate and further examine these approxi-

<sup>\*</sup>These points may be found beautifully elucidated in Remsen's Theoretical Chemistry, p. 299.

<sup>†</sup> Kerner, Gaspard and Stich. (Although these were supposed to exist as early as 1789.—Witthaus.)

mates became a problem of unusual importance. At Dorpat, in Russia, six theses were written in four years, 1866–1870.\* The researches of Selmi in toxicology required of him a study of these noxious substances. Upon obtaining them in sufficient amount to note their physiological effects he saw their likeness to vegetable alkaloidal poisons; so significant were these observations that they excited vigorous controversy and rigorous criticism. After they had become established, the name Ptomaine was given to them, from Greek roots, meaning "carcase—matter." The labors of Armand Quatier,† of France, and Lewis Brieger,\* of Germany, in this direction, have been of vital consequence to the progress of etiology.

Brieger's recent studies in this direction have simplified the

processes for their extraction.

"The putrid liquids are brought to boiling (100° C.), separated from  $d\acute{e}bris$ , then immediately precipitated with bichloride of mercury (corrosive sublimate), then filter. Wash the precipitate, and subject it to the action of sulphuretted hydrogen until all the mercury is precipitated, then filter and concentrate the liquid to a syrup; wash with absolute alcohol; soon long needle-shaped crystals appear, insoluble in absolute alcohol, but soluble in water, weak alcohol, benzine, chloroform and the like."

The processes for alkaloids given by Dragendorff, Stas, Otto and Selmi,† are used for their complete separation. There is no method of immediately distinguishing the animal from the vegetable alkaloids although both the ferricyanide and nitroprussiate of potassium have been said to possess the power to do so.

The physiological effects of the alkaloids, when derived from a cadaver exhumed one hundred and twenty days after burial, were as follows: The ptomaines extracted by ether, injected into a medium-sized dog under the skin, after twenty minutes caused convulsive trembling, irregular contraction of the pupil, increased pulse, slight hyperthæmia, congestion of the external ear, and languor. In forty minutes spasm of the facial muscles and the limbs, diminished respiration, and death in forty-four minutes. The autopsy revealed immobility of the auricle, ir-

† Blythe, p. 212, et seq.

<sup>\*</sup>Professor, Hugomenq, of Lyons, France, Bibliog. Animal. Alk.; also Index Medicus and Catalogue Surgeon-General's Office, U. S. A.

regular contraction of the *left* ventricle, the right filled with blood, and the *left* side of the heart empty (diastole). The quantity used was one gramme. The *chloroform extract* exhibited in similar amount and manner, to a dog of nearly the same size, produced hurried respiration, rapid pulse, and congested helices of the ear. Recovery to normal condition twenty minutes afterward. A smaller amount than one gramme administered to a frog affected the animal as follows: slight nervousness, flaccidity of the muscles, loss of the motor power under galvanic stimulus, retained sensibility. The ptomaine separated by alcohol caused in a frog uncertain movements, irregular dilatation, cutaneous insensibility, followed by general relaxation.\*

Physiologically the ptomaines divide themselves into three groups, innocuous, not fatal, and virulent. Parvoline and neuridine belong to the first group, cadaverine and putrescine to the second group, mydaleine, neurine, hydrocollidine, and sepsine to the third group.

Lecithin, one of the living leucomaines, immediately after life ceases becomes broken up into choline, which, in the slow process of human putrefaction, remains until the seventh day At the end of the third day neurine appears, which is detected until the fourteenth day. With this alkaloid two others-cadaverine and putrescine—then make their appearance, both possessing a very disagreeable odor; the first is viscid, the latter thin. Saprine also appears with cadaverine. At the end of seven days mydaleine makes its appearance; it is virulently poisonous ( $\frac{8}{100}$  grain, or 0.005 gramme, of the chloride produces terrible death to guinea-pigs). Closely allied to neuridine is neurine, which resembles muscarine (or mushroom poison) in its toxic effects. The physiological behavior of mydaleine is, briefly: profuse diarrhoea, vomiting, intestinal inflammation; the heart ceases in diastole, contraction of abdominal muscles, and the head is violently drawn upon the chest, back arched outward: death takes place with the eyes closed, as in sleep. Neuridine causes paralyses of the posterior columns of the cord, followed by convulsions, with emptying of the bowels, bladder, etc. A complete exposition of these bodies may be found in the recent works of L. Brieger.

<sup>\*</sup>Brown, A. M.: Ptomaines and Leucomaines, London, 1887.

<sup>†</sup> Brieger: Ueber Ptomaine, in three volumes. Berlin, 1887.

These discoveries led to the comparative therapeutic effect of vegetable and animal poisons, as they were so similar, while there were not wanting instances in which the identical symptoms were observed, when there was positive knowledge of the inception of no vegetable alkaloid or the using of decayed flesh foods. As a consequence, an inquiry was started respecting the possible source of these affections. The degeneration of dead albuminoids is plainly shown in the study of the ptomaines, while the results of retained urine extractives, under the general name of uræmic poisoning, have long been recognized.

From what we now know of the production of vegetable alkaloids one is inclined to regard them as a process of generation, upon the *upward* scale of chemical constitution of albuminoids; while the degenerated extractive matters of the animal body albuminoids, having a simpler chemical constitution,\* (occupy the descending scale) are less acutely toxic, although on account of their cumulative effect they seem more virulent than they really are, *e. g.*, uræmic convulsions and coma. See Table II.

The possibilities of discovering this desirable data seem near at hand: with it an attractive vista of physiology is disclosed.

It has been found that if nucleine, obtained from an unhatched fecundated egg, has slightly acidulated water added, it breaks into the uric compounds, while with an unhatched unfecundated egg no such disintegration takes place, both being placed at incubation temperature.

In the fecundated egg the conditions of heat produce a chick, otherwise only poisonous degenerated albuminoid compondus are the result. This chick lives without external air, and may be termed, as Gautier suggests, an-aërobic; so that putrid elements may be produced (without oxygen from the atmosphere) in the shell. Skilful observations have convinced Gautier; that the human body contains compounds capable of living putrefactively or an-aërobically to the extent of one fifth, while the other four-fifths of the excretions depend for their elimination

<sup>\*</sup>Muscarine obtained from fish, horse, etc., is identical with the alkaloid of agaricus muscarius (mushroom).

<sup>†</sup> Kossell: Deut. Chem. Gess., 1886, p. 316.

<sup>#</sup> Gautier: Leucomaines, Paris, 1886.

upon the inspired atmosphere for their supply of oxygen. Further research, prompted by the conduct of albumen, gave rise to the discovery of certain animal alkaloids based upon the urinary approximates obtained from the living body. These bodies were named by Gautier Leucomaines.

They may be divided into two series: I. Those of uric acid: 1. Betaine, C<sub>5</sub>H<sub>11</sub>N<sub>1</sub>O<sub>2</sub>. 2. Adenine, C<sub>5</sub>H<sub>5</sub>N<sub>5</sub>. 3. Guanine, C5 H5 N5 O. 4. Hypo-xanthine, C5 H4 N4 O. 4. Xanthine, C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>O<sub>2</sub>. 5. Pseudo-xanthine, C<sub>4</sub>H<sub>5</sub>N<sub>5</sub>O. 6. Carnine, C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>. II. Those of creatinine: 1. Xantho-creatinine, CRUSO-creatinine, C, H, N, O. AMPHI-creatinine, C5H10N4O. C. H. N.O.

There are still other leucomaines which have been unnamed; the sources of their recovery are from the urine, blood, spleen, intestine, fish, saliva, and venomous reptiles. Many of these extractives may be obtained from the upper boiling liquors of any bone-rendering establishment, and separated by the use

of ether, hot and cold absolute alcohol.

Those of the creatinine group mentioned above are exceedingly interesting because obtained from fresh meat. The following method \* has proved valuable to me.

Soak finely hashed meat in water made strongly acid with oxalic acid for thirty-six hours in the cold; filter by usual means (pump); boil filtrate thoroughly, which precipitates certain albumens. Evaporate the filtrate from this at 50° C., and treat with cold absolute alcohol. Evaporate, treat the syrupy extract with hot absolute alcohol, and allow the clear liquid to cool; add pure ether. In twenty four hours or so, crystals form. Transfer them to a filter, drain them, wash the filter with cold absolute alcohol, and stand the filtrate aside (marked P.).

Wash the remaining crystals on the filter with hot absolute alcohol; the filtrate contains xantho-creatinine. The remaining crystals are washed with boiling water, in which they dissolve. When the filtrate cools (at 17° C.), a white precipitate separates, which is isolated rapidly by filtration, from which substance amphi-creatinine may be obtained. The filtrate upon concentration yields cruso-creatinine.

All the solutions marked "P" are thrown together, concen-

<sup>\*</sup>Gautier: op. cit.

trated, and treated with boiling acetate of copper to eliminate the *pseudo*-xanthine by the usual processes. Most of these leucomaines respond to the general alkaloidal tests; they may, however, be distinguished by the application of them to their concentrated oxalic or chlorhydric solutions.

Xantho-creatinine is soluble in cold water, and in hot absolute alcohol; it forms crystals with zinc chloride, and is precipitated by tannin. It forms crystals with auric and mercuric chlorides.

CRUSO-creatinine is soluble in hot water, forms needle-crystals with platinic chloride, rounded masses with auric chlorides, and is precipitated in the cold by acetate of copper.

AMPHI-creatinine is soluble in cool (17° C.) water. It forms crystals with hydrochloric acid (like salt), is soluble; also soluble crystals with chloride of platinum.

Pseudo-xanthine is soluble in cold and hot alcohol (absolute). Heated with acetate of copper, it is precipitated when the copper is removed by hydrogen sulphide. The usual tests for xanthine are responded to.\* Its absolute character is known from its chemical formula. The therapeutical effects of xantho-creatinine are, in animals, extreme fatigue, purging, vomiting, depression, somnolence † and convulsions, when pushed in large doses. The other members of this group have not been sufficiently studied. See Table III.

Now these elements belong to series which have their origin in the body, and can only be eliminated by the *poietic* organs and the lungs. One-fifth of these extractives must be rendered harmless without the use of external (oxygen) air. When this equilibrium is destroyed it will certainly make the patient sick. This equilibrium is not only destroyed, but the processes set up are catalytic and manufacture normal products in undue quantities. The lack of lung power or capacity soon evinces itself by extreme exhaustion, the insufficient supply of food, or the too great indulgence in *proteid* substances.

The (catalytic) fermentative action, similar to leaven, may be the means of disseminating diseases by indigestion.

<sup>\*</sup>Neubauer and Vogel, op. cit.

<sup>†</sup> Witthaus, in Woods' Handbook of Medical Science, 1888, vol. vi., p. 64.

<sup>‡</sup> It is well known that grape-sugar will produce alcohol and acetone, and it is equally well known that acetone has been found in bodies dead from diabetic diseases. Ethyl-diacetic acid is found in urine,

From what we have learned of the ptomaines they generate cramps, diarrhea, and algidity when received into the circulation; similar symptoms arise from non-eliminated, but normal leucomaines, it is then but a step in bio-chemics to attribute some, at least, of our infectious intestinal disorders to these chemical synthetical combinations.\* It is useless to detail the method of the inception of maladies by means of food and liquids.

The correlation of the sciences demands that no one theory of disease arrogate to itself a complete pathology. The germ theory is unable to produce a specific microbe for each disease. However, here is a clear chemical proposition, that harmless compounds, when brought in contact with others equally harmless in themselves, are sometimes able to produce; by that yet unknown, (complete) law of affinity, approximates toxic to the animal economy.

All the theories mentioned in the beginning of this paper, when taken as a whole, present a composite clinical cause for numerous diseases.

The practical outcome of this study is that we apply to the individual patient just what experience has taught: a brisk catharsis, followed by the intelligent use of the alkaloids, in order to save the system the toil of their elaboration, followed by the use of tonics rich in oxygen.

It may be confidently asserted that there are sufficient chemical facts for the putrefactive etiology of complaints, doubtless to be confirmed by further and future precise physiological research.

<sup>\*</sup>Aitkin, Sir Wm.: Animal Alkaloids, London, 1887.

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Author.		Gautier and Etard,	Gautier and Etard,	Gautier and Etard,	Guareschi and Mosso	Nencki,	Brieger,	Brieger,	Brieger,	Brieger,	Brieger,	Brieger,	Sundeburg, H. & B.	Pouchet,	Pouchet,	Pouchet,	Brieger,	Brieger,	Brieger,	Brieger,	Victor Vaughan,
.912	COT		Toxic				Toxic		:		Toxic	Toxic	Toxic		Toxic	Toxic				:	Toxic
.991	nog	Fish	Fish	Beef	Beef	Artif.	Human	Human	Human	Human	Human	Human	Human	Cod	Beef	Beef	Human	Human	Reptile	Horse	Milk
	Pt013	:			Precip.		Precip.	Crystal.	Crystal.			Crystal.	Precip.	Crystal.	Crystal.	•	: :				
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Chemical	constitution,				IsoC <sub>6</sub> H <sub>5</sub> C <sub>2</sub> H <sub>4</sub> NH <sub>2</sub>		S(CH <sub>3</sub> )C <sub>2</sub> H <sub>3</sub> NOH <sub>2</sub>		8(CH <sub>3</sub> )C <sub>2</sub> H <sub>3</sub> OHNOH <sub>2</sub>									Amido-acid,	Oxide, choline,		Dinitro-benzole,
	Wat	:	:	1	:	:	;	:	. :	:	1-1	:		*	:	:	:	:	:	:	-
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	PTOMAINES,	Parvoline,	Hydrocollidine	0.4	0	Collidine,	Neuridine,	Cadaverine,	Putrescine,	Mydaleine,	Neurine,	Choline,	Muscarine,	Gadinine,	0-	Que.	Tetanine,	Typhoidine, .	Mytilotoxine, .	Mydilotoxine,	Tyrotoxicon

TABLE III.—LEUCOMAINES.

Precip.   Copper.   Precip.   Copper.   Precip.   Copper.   Precip.   Copper.   Precip.   Copper.   Precip.   Copper.   Copp	Lead.		nu	- w		u		u			
Precip.         White.           Precip.         Yellow           White.         White.           White.         Yellow           Oryst.         Cryst.         Yellow           Precip.         Yellow         Yellow           Toxic         Yellow         Yellow			Gold		Alc.		Alc.	Chlor.	Еіћег, Съјог.	Water, Сhlor.	Chlor. Chlor.
Precip.         White.           Precip.         Xellow           White.         Toxic           White.         Yellow           Chyst.         Cryst.         Red         Toxic           Yellow         Yellow         Yellow           Precip.         Xellow         Yellow	:	:						Hot	2 Hot	-	०२
Precip.         Xellow           White.            Red         Toxic           White.            White.            Cryst.         Cryst.         Red         Toxic           Toxic          Yellow            Precip.          Cryst.         White.            Precip.          Yellow            Toxic          Yellow				-	Sol.	**		**		Cold	1 Cold
White.   Red   Toxio   White.   Red   Toxio   White.   Red   Toxio	:	Cryst.		-	•			Hot		Hot	2 Hot
Ned   Toxio   Sed   Toxio   White.   White.   Sed   Toxio   Cryst.   Cryst.   Cryst.   Cryst.   White.   Cryst.   Cryst.   White.   Cryst.   White.   Cryst.   Crys		. Sol.	:	-	:	:		Cold		Cold	1 Cold
White.   White.   White.   White.     White.	: : :	. Cryst.				Sol	Sol			4 8 Cold	8 Cold
Oryst.         Oryst.         Red         Toxio           Toxio         Toxio         Toxio         Toxio           Toxio         Toxio         Toxio         Toxio	Precip.	Cryst.	:			:		:	:	1 2 Cold	2 Cold
Coryst.         Gryst.         Red         Toxio           Toxio         Toxio         Toxio         Toxio           Precip.         Toxio         Toxio         Toxio		.   Cryst.			Hot	Hot			Cold Insol	g Cold Insol	Cold Insol
Precip		st	Cryst.		Hot	Hot	Insol.	:	1 Cold Insol	4 1 Cold Insol	1 Cold Insol
Precip Cryst. White  Precip Xellow		t. Cryst.	Cryst.		Insol.		Insol.		Hot Insol	4 Hot Insol	Hot Insol
Toxic	. Cryst.	st	Cryst.		-	Insol.	:		4 Cold Insol	7 4 Cold Insol	4 Cold Insol
Toxic	Prec	:	in		Cold	Cold and Hot	Insol.   {	-:-	1 Insol {	5 1 Insol {	1 Insol {
			:		:	:				10	
					:					11	
Yellow Reptile	. Precip	Precip.	:			Sol.		Sol.	1 Insol. Sol.	5 1 Insol. Sol.	1 Insol. Sol.